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(54) **Elemental diets for liver diseases**

(57) An elemental diet for the nutrition of patients suffering from liver diseases comprises amino acids (and may also comprise carbohydrate, fat, vitamin and mineral), the diet containing at least isoleucine, leucine, valine, phenylalanine, tyrosine, tryptophan, threonine, glycine, serine and arginine in amounts such that the molar ratio of isoleucine + leucine + valine + arginine to phenylalanine + tyrosine + tryptophan is from 50:1 to 60:1, the molar ratio of isoleucine + leucine + valine + arginine to glycine + serine + threonine is from 4:1 to 5:1, and the molar ratio of arginine to glycine + serine + threonine is from 0.8:1 to 1.0:1.

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SPECIFICATION

Elemental diets for liver diseases

This invention relates to new elemental diets for the nitrition of patients suffering from liver diseases.

The basic therapy for liver diseases is diet therapy. It has heretofore been thought that the most suitable diet for liver diseases is one which prevents catabolism with high energy, which has a high protein content and which promotes the regeneration of liver cells for the purpose of restoring their hepatic function. However, depending on the severity of the hepatic disorder, unless the amount of protein to be ingested is restricted, substances which would cause hepatic encephalopathy, such as ammonia, amines, short-chain fatty acids, etc., accumulate as the result of the decrease in the metabolic function of the liver, and hence the disease is aggravated. Therefore, for patients with whom oral ingestion is possible, a low protein diet is used. However, since it is difficult to inhibit the catabolism of somatic protein if the diet is used for a long period of time, a medium level protein diet has been used in combination with lactulose, antibiotics, etc.; however, side effects such as diarrhoea, microbisme selectionné et substitué, renal insufficiency, etc., are too grave to be neglected, and thus an adequate effect cannot be expected. Further, in the case of more seriously affected patients in the case of whom oral ingestion is not possible, only passive therapy, which seeks to improve encephalopathy and protect the liver by the intravenous administration of glucose, is used.

An elemental diet which contains amino acids, carbohydrates, fats, vitamins, minerals, etc. has been proposed for patients in the case of whom oral ingestion was not possible (Stephens, R. V., et al, Ann. Surg., *170* 642 (1969), but this diet is hardly suitable for the treatment of liver diseases. Furthermore, even by intravenous hyperalimentation, as long as a conventional amino acid composition is employed, appropriate nutritional management cannot be achieved.

In recent years, researches on the pathophysiology of various diseases, especially on the blood amino acid patterns, have been increasingly carried out, and accordingly, in the case of liver diseases, the alterations in plasma amino acids have been made clear. For example, the concentration of branched-chain amino acids such as valine, leucine, isoleucine are lower as compared to the normal level, whereas the concentrations of aromatic amino acids such as phenylalanine, tyrosine and tryptophan and of sulphur-containing amino acids such as methionine, taurine, etc., are increased.

Such abnormality in the plasma amino acid level is believed to be due to the decrease of the metabolic function of the liver. Recently, there has been proposed a method for treating encephalopathy by rectifying the abnormality of the plasma amino acid level in the case of hepatic insufficiency, by the intravenous administration of an amino acid solution (see Fischer, J. E. et al., Surgery, *80* 77 -91 (1976)).

We have now developed an elemental diet for the purpose of the nutritional management of patients with a serious liver disease.

According to the present invention, there is provided an elemental diet containing amino acids, wherein the amino acids are at least isoleucine, leucine, valine, phenylalanine, tyrosine, trytophan, threonine, glycine, serine and arginine in amounts such that the molar ratio of isoleucine + leucine + valine + arginine to phenylalanine + tyrosine + tryptophan is from 50:1 to 60:1, the molar ratio of isoleucine + leucine + valine + arginine to glycine + serine + threonine is from 4:1 to 5:1, and the molar ratio of arginine to glycine + serine + threonine is from 0.8:1 to 1.0:1.

Preferably, the elemental diet contains at least the essential amino acids together with alanine, arginine, glycine, histidine, proline and serine, in the following amounts:

Amino Acid	*Mole %*
Isoleucine	13.25–16.19
Leucine	16.25–19.87
Valine	13.86–16.94
Lysine	5.36– 6.55
Methionine	0.79– 0.97
Phenylalanine	0.71– 0.87
Threonine	3.68– 4.50
Tryptophan	0.27– 0.33
Alanine	11.04–13.50
Arginine	10.02–12.24
Glycine	5.76– 7.04
Histidine	1.99– 2.43
Proline	4.56– 5.58
Serine	2.46– 3.00
Total	100

The diet may contain one or more of carbohydrate, oil or fat, vitamin and mineral. Furthermore, if desired, additives such as fungacides, emulsifiers, etc., may also be incorporated into the diets.

The amino acids rather than being used as such may be used as derivatives or adducts which may be assimilated as amino acids *in vivo,* and may thus be used as salts of mineral acids such as hydrochloric acid, as salts or organic acids such as acetic acid, malic acid, etc., as peptides, as N-acylates, as hydrates, etc. In such a case, each amino acid derivative or adduct may be incorporated into the diet in an amount to satisfy the above composition as calculated as the free form of the amino acid. Thus, for example, amino acids such as lysine, histidine, arginine, etc., may be used as salts such as a hydrochloride, an acetate, etc.

The amino acid content of the composition is usually 10-20% by weight or so.

The carbohydrate used in this invention is, for example, dextrin. Monosaccharides, oligosaccharides, etc. may also be employed. The amount to be used expressed in % by weight, is generally 70-80% or so.

The oils or fats used in this invention are, for example, soybean oil, corn oil, cotton seed oil, etc. The amount to be used, expressed in % by weight, is generally 2-4% or so, and by using such a low amount of fat, the solubility or emulisfiability may be enhanced, and also the occurrence of diarrhoea due

to fat degradation, etc., may be minimised.

The vitamins used in this invention are, for example, Vitamin A (e.g. retinol acetate), Vitamin B_1 (e.g. thiamine hydrochloride), Vitamin B_2 (e.g. riboflavin phosphate sodium), Vitamin B_6 (e.g. pyridoxin hydrochloride), Vitamin B_{12} (e.g. cyanocobaltamine), Vitamin C (e.g. ascorbic acid), Vitamin D_2 (e.g. argocalciferol), Vitamin E (e.g. tocopherol acetate), Vitamin K_1 (e.g. phytonadione), calcium pantothenate, nicotinic acid amide, biotin, folic acid, and choline bitartrate.

The total amount of vitamins used is generally 100-200 mg or so per 100 g of the nutrient composition.

The minerals used in this invention are, for example, iron (e.g. as iron gluconate dihydrate), copper (e.g. as copper sulphate pentahydrate), manganese (e.g. as manganese sulphate pentahydrate), zinc (e.g. as zinc sulphate heptahydrate), potassium (e.g. as potassium gluconate or potassium chloride), iodine (e.g. as potassium iodine), sodium (e.g. as sodium citrate dihydrate), calcium (e.g. as calcium glycerophosphate), and magnesium (e.g. as magnesium sulphate heptahydrate).

The total amount of minerals used is generally 4000-7000 mg or so per 100 g of the nutrient composition.

Since, in the liver diseases, especially in liver cirrhosis, a reduction in exchangeable potassium (Ke) is observed, the amount of potassium used may be greater as compared to a conventional nutrient or elemental diet. Desirably, about 1500-2500 mg of potassium gluconate or about 500-1000 mg of potassium chloride are employed per 100 g of the nutrient composition.

Since zinc is expected to have the effect of protecting liver cell membranes it is better to use zinc in an amount greater than the conventional level. Therefore, 15-25 mg of zinc sulphate heptahydrate per 100 g of the nutrient composition is preferred.

When a composition of this invention is used as a product, by employing a fungicide such as potassium sorbate, and an emulsifier such as polysorbate, soybean phospholipid, etc. as additives, the proliferation of bacteria in powder or solution may be inhibited. Furthermore, since the composition is easily dissolved or emulsified, its administration by the use of a tube or orally is relatively easy.

Where the nutrient of this invention is to be administered to a patient with a liver disease, it is more easily administered when it is emulsified and homogenized; this is preferred also from the aspect of digestion and absorption.

The product of this invention may be administered either intraintestinally or orally. When administered intraintestinally using a tube, it is advisable to use it as a solution, e.g. about 5-40w/v% in water, preferably lukewarm water.

The diet of this invention may be widely used as a nutrient for the treatment of liver diseases for the purpose of improving poor hepataic functioning, for instance, for nutritional management before and after operations on patients with liver cirrhosis, patients with hepatoma, patients with chronic hepatitis, etc.; for the prevention of a hepatic coma and the awakening of a patient from a hepatic coma in the case of hepatic insufficiency; and for the promotion of liver regeneration in the case of liver excision.

The invention will now be illustrated by the following Examples wherein Examples 2, 3 and 4 relate to experiments on the effectiveness of a diet according to the invention as a nutrient for the treatment of liver diseases, using animal models.

Example 1

Materials set forth in Table 1 were uniformly dry mixed.

Table 1 Composition of Elemental Diet for Liver Disease (per 100 g)

dextrin	74.32 g	choline bitartrate	105.0mg	L-methionine	0.146 g
Soybean oil	3.50 g	iron gluconate dihydrate	11.52mg	L-phenylalanine	0.146 g
phytonadione	55.0 µg	copper sulfate pentahydrate	1.02mg	L-threonine	0.545 g
retinol acetate	0.310mg	manganese fulfate pentahydrate	1.59mg	L-tryptophan	0.070 g
thiamine hydrochloride	1.121mg	zinc sulfate heptahydrate	19.70mg	L-alanine	1.222 g
riboflavin phosphate sodium	1.209mg	magnesium sulfate heptahydrate	507.0mg	L-arginine	2.170 g
pyridoxin hydrochloride	0.839mg	Potassium iodine	40.8ug	glycine	0.538 g
cyanocobalamine	2.70 µg	potassium chloride	991.5mg	L-histidine	0.383 g
ascorbic acid	29.25mg	potassium gluconate	2.110 g	L-proline	0.652 g
ergocarliciferol	4.78µg	calcium glycerophosphate	1.602 g	L-serine	0.321 g
tocopherol acetate	20.65mg	sodium citrate dihydrate	980.8mg	soybean phospholipid	170 mg
calcium pantothenate	2.06mg	L-isoleucine	2.162 g	polysorbate 80	50 mg
nicotinic acid amide	4.13mg	L-leucine	2.652 g	potassium sorbate	150 mg
biotin	49.0 µg	L-Valine	2.019 g	L-ascorbyl stearate	2 mg
folic acid	0.165mg	L-lysine acetate	1.374 g	anhydrous citric acid	1015 mg

When employed orally, the above-described mixture was either formed into a paste using water, or dissolved in a suitable amount of water. At this time, natural and/or synthetic food flavours such as chocolate, peppermint, custard, pistachio, etc., may also be mixed and incorporated into the mixture.

When employed intraintestinally, a standard solution for administration may be obtained by dissolving 80 g of the above-described mixture in lukewarm water and making the total volume up to 300 ml (26.7% w/v). Furthermore, depending on necessity, solutions of varied concentrations of 5-30% w/v may be prepared and put into bags for administering, and each solution may be administered to the duodenum or the jejunum of a patient via a catheter.

Example 2

Awakening Effect on Ammonia-induced Coma

The mixture given in Example 1 was employed as a 25% w/v solution (Test Group 1). One comparison control was our commercial elemental diet "Elental" (Registered Trade Mark) (Test Group 2), and another was one in which the amino acid portion of "Elental" was replaced by the composition "FO-80" (see JP-118839/1976-A) (Test Group 3). The test animals used were SD strain male rats weighing about 240 g. After fasting overnight, the liver was excised (by 70%), and a gastric fistula tube was provided as an administration route for the elemental diet. Each solution was continuously infused at a rate of 7.3 ml/kg/hr up to 24 hours after the liver excision, and at 10.4 ml /kg/hr thereafter. After 48 hours after the liver excision, 2.6 ml /kg of a 10% w/v ammonium chloride solution was intraperitoneally administered, and the coma conditions were checked by the presence of a righting reflex. The results are shown in Tables 2 and 3.

Table 2

	n	mortality (%)	comatose time (min)
Test Group 1	6	0	38 ± 9^{a}
Test Group 2	5	40	77 ± 16^{b}
Test Group 3	6	33	58 ± 24^{b}

a, b : Means within the same column and followed by the same superscript letter are not significantly different. ($P < 0.05$, $\bar{x} \pm SD$)

Table 3

	n	$\frac{BCAA}{AAA}$	$\frac{BCAA}{AAA+Tau+Met}$	$\frac{BCAA+Arg}{Thr+Ser+Gly}$
Normal control	5	2.87 ± 0.35^{ab}	0.60 ± 0.05^{b}	0.85 ± 0.11^{b}
Test Group 1	6	3.92 ± 1.64^{a}	0.97 ± 0.29^{a}	1.06 ± 0.18^{b}
Test Group 2	3	1.57 ± 0.30^{ab}	0.44 ± 0.06^{b}	0.40 ± 0.07^{a}
Test Group 3	4	1.94 ± 0.90^{b}	0.62 ± 0.18^{b}	0.52 ± 0.16^{a}

BCAA : branched-chain amino acid (sum of Leu, Ile and Val)

AAA : aromatic amino acid (sum of Phe, Tyr and Trp)

a,b,c: $P < 0.05$

As shown in Table 2, the results for Test Group 1 were better than those for Test Groups 2 and 3 in respect of death rate and coma period. Furthermore, as shown in Table 3, the molar ratio of the plasma free amino acid levels immediately after awakening from the coma (especially the ratio of the branched-chain amino acids to the aromatic amino acids, and moreover the ratio of the branched-chain amino acids to the sum of the aromatic amino acids, methionine and taurine) were in co-relationship with the results in Table 2.

Example 3

Promotion of Liver Regeneration

The test solutions as in Example 2 were employed, and Example 2 was repeated. As the test animals, SD strain male rats (weighing about 240 g) were employed. After the liver excision, each test solution was administered as in Example 2, and 5 days after the liver excision, the liver regeneration ratio was measured. The results are shown in Table 4.

Table 4

	n	Liver Regeneration Ratio %
Test Group 1	9	89.4±23.7 [a]
Test Group 2	4	53.1±20.7 [b]
Test Group 3	5	63.4±9.1 [b]

$$\text{Liver Regeneration Ratio} = \frac{\text{Regenerating Liver (at autopsy)} - \text{Residual Liver (estimated at excising)}}{\text{Excised Liver}} \times 100$$

a, b : $P < 0.05$

From Table 4, it can be seen that liver regeneration is promoted in the order Group 1 > Group 3 > Group 2.

Example 4

Nutritional Effect on Rats with Chronic Hepatic Disorder

The test solutions as in Example 2 were employed. The test animals used were SD strain male rats weighing about 150 g. A 60% v/v solution of carbon tetrachloride in olive oil was administered in an amount of 1 ml /kg, twice a week for 10 weeks, to induce experimental hepatic fibrosis, and rats from which about 70% of the liver has been removed were used as models with chronic hepatic disorder. The administration of the test solution was conducted similarly as in Example 2, and continued for 7 days. The results are shown in Table 5.

Table 5

	n	survival ratio %	nitrogen balance mgN/3 days	hepaplastin test %
Normal control	5	-	-	70.8±8.4 [a]
Test Group 1	7	100	-34.2±83.5	72.0±6.5 [a]
Test Group 2	7	57	-122.6±121.5	50.0±13.1 [b]
Test Group 3	7	100	-87.8±102.7	68.0±15.1 [a]

a, b : $P < 0.05$

As evident from Table 5, there were deaths in the case of Group 2, whereas the rats of the other Groups recovered successfully. The nitrogen balance was good in Group 1. In a hepaplastin test, which indicates the synthetising activity of blood coagulation proteins, the recovery was in the order Group 1 > Group 3> Group 2. Furthermore, Group 1 had a better effect in improving the molar ratio of the plasma amino acid level as compared with the other groups (see Table 6).

Table 6

	n	$\frac{BCAA}{AAA}$	$\frac{BCAA}{AAA+Tau+Met}$	$\frac{BCAA+Arg}{Thr+Ser+Gly}$
Normal control	4	2.38±0.05 [a]	0.81±0.03 [a]	0.70±0.07
Test Group 1	5	1.99±0.14 [b]	0.63±0.05 [b]	0.67±0.18
Test Group 2	4	1.56±0.10 [d]	0.50±0.07 [c]	0.56±0.07
Test Group 3	6	1.76±0.10 [c]	0.59±0.06 [c]	0.56±0.06

Abbreviations are same in Table 3. a,b,c,d : $P < 0.05$

CLAIMS

1. An elemental diet containing amino acids, wherein the amino acids are at least isoleucine, leucine, valine, phenylalanine, tyrosine, trytophan, threonine, glycine, serine and arginine in amounts such that the molar ratio of isoleucine + leucine + valine + arginine to phenylalanine + tyrosine + tryptophan is from 50:1 to 60:1, the molar ratio of isoleucine + leucine + valine + arginine to glycine + serine + threonine is from 4:1 to 5:1, and the molar ratio of arginine to glycine + serine + threonine is from 0.8:1 to 1.0:1.

2. An elemental diet as claimed in claim 1, containing the following amino acids in the following amounts:

Amino Acid	*Mole %*
Isoleucine	13.25–16.19
Leucine	16.25–19.87
Valine	13.86–16.94
Lysine	5.36– 6.55
Methionine	0.79– 0.97
Phenylalanine	0.71– 0.87
Threonine	3.68– 4.50
Tryptophan	0.27– 0.33
Alanine	11.04–13.50
Arginine	10.02–12.24
Glycine	5.76– 7.04
Histidine	1.99– 2.43
Proline	4.56– 5.58
Serine	2.46– 3.00
Total	100

3. A modification of a diet as claimed in claim 1 or 2, wherein one or more of said amino acids is in the form of a derivative or adduct thereof (the amount of said derivative or adduct being based upon the assumption that it is in the form of its free amino acid).

4. A diet as claimed in any of claims 1 to 3, wherein said amino acids (or derivative or adduct thereof) are present in the composition in a total amount of from 10 to 20% by weight.

5. A diet as claimed in any of claims 1 to 4, wherein the diet contains one or more of carbohydrate, oil ro fat, vitamin and mineral.

6. A diet as claimed in any of claims 1 to 5, wherein the diet contains one or more of preservative, emulsifier, flavouring, seasoning and water.

7. A diet as claimed in claim 1, substantially as hereinbefore described.

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